TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
H 10019 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/012930	15.11.2004	14.11.2003
International Patent Classification (IPC) or national classification and IPC		
A61 K48/00, C12N15/861		
Applicant		
HOLM, Per Sonne		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____ , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

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International application No.
PCT/EP2004/012930

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-82 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-70 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/25-25/25 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	15-19,27-29,41,42,44-46,57-70	YES
	Claims	1-14,20-26,30-40,43,47-56	NO
Inventive step (IS)	Claims	57-70	YES
	Claims	15-19,27-29,41,42,44-46	NO
Industrial applicability (IA)	Claims	1-70	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

V.1. This report makes reference to the following documents:

D1: US 2002086411 (Holm, P. S.)

D2: Wong, H. K. and Ziff, E. B. (1994) Complementary functions of E1a conserved region 1 cooperate with conserved region 3 to activate Adenovirus serotype 5 early promoters. J. Virol. 68, No. 8, 4910 - 4920.

D3: Howe, J. A. et al. (2000) Evaluation of E1-mutant adenovirus as conditionally replicating agents for cancer therapy. Molecular Therapy 2, No. 5, 485 - 495.

D4: WO 03/033692 (Holm, P. S.)

V.2. **Novelty** (PCT Article 33(1) and (2))

V. 1. D1 discloses the use of an E1-deficient adenovirus for producing a drug for the treatment and/or prevention of a tumor (page 1 [0011]). An E1-deficient adenovirus is

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

understood to mean an adenovirus that is deficient preferably in the E1A and/or the E1B protein (page 1 [0019]). The E1A-deficient adenovirus is capable of replicating in tumor cells that have YB-1 in the cell nucleus (page 2 [0018] - [0020]). Furthermore, the adenovirus described in D1 can contain a DNA sequence that codes for YB-1 (page 1 [0009]) and that is under the control of a tumor-specific promoter (page 2 [0028], last sentence) and enables the expression thereof, preferably in the cell nucleus (page 2 [0020], lines 8-10). D1 also describes a pharmaceutical compound that contains additional components effective against tumors (page 2 [0024] such as, for example, cytostatics or ribozymes, and/or that can be used in conjunction with other therapeutic approaches such as radiation and/or chemotherapy (page 2 [0026]).

V. 2. In view of the disclosure in D1, the subject matter of claims 1-14, 20-26, 36-40, 43 and 47-56 cannot be regarded as novel within the meaning of PCT Article 33(1) and (2) (see the text passages indicated above).

V. 3. Figure 1 in D2 shows various mutants of the adenoviral E1A protein that affect primarily its CR1 region, including the construct dl347, which corresponds almost entirely to the dl520 disclosed in the

present application. The protein derived therefrom (intrinsically) has the properties indicated in claims 30-35.

Consequently, these claims cannot be regarded as novel within the meaning of PCT Article 33(1) and (2).

V. 4. The subject matter of claims 15-19, 27-29, 41, 42, 44-46, and 57-70 appears to be novel within the meaning of PCT Article 33(1) and (2).

V.3. **Inventive step** (PCT Article 33(1) and (3))

V. 1. D1, which is regarded as the closest prior art, discloses the use of an E1-deficient adenovirus, said virus preferably being deficient in the E1A and/or E1B protein, in order to produce a drug for the treatment and/or prevention of a tumor (see above).

V. 2. The subject matter of claims 15-19 differs therefrom in that the viral oncogene protein E1A "has one or more deletions, ..., which includes the deletions of the CR3 region and deletions of the N-terminus and deletions of the C-terminus".

V. 1. That means producing an adenovirus, the E1A gene of which is mutated, in order to be able to express an E1A protein which, depending on its purpose, does or does not bind to RB.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V. 2. Figure 1 in D2 shows different mutations that affect the CR1, CR2 and CR3 regions of the adenoviral E1A protein. Therefore it is assumed that a person skilled in the art proceeding from the prior art has enough information in order to modify the adenovirus described in D1, and therefore to solve the above-mentioned problem.

V. 3. D3 discloses adenoviruses that can carry out various mutations in the E1 region and, in association therewith, can have a selective cytopathic effect on tumor cells *in vitro* and, furthermore, are capable of inhibiting tumor growth *in vivo*: E1Ad101/07 has a cytopathic effect on a series of different tumor cells, while primary cells are not affected (figure 6, table 1; page 493, left-hand column, second paragraph).

V. 4. Accordingly, the subject matter of claim 27 appears to be obvious to a person skilled in the art, and consequently this claim cannot be acknowledged as involving an inventive step within the meaning of PCT Article 33(1) and (3).

V. 5. D4 discloses the use of the adenoviral E2 late promoter for the regulation of the gene expression of cells that have YB-1 in the cell nucleus, such as cancer cells.

V. 1. D1 already mentions the use of tumor-

specific promoters for the replication of YB-1.

Proceeding from the advantages associated with using E2 late promoters as mentioned in D4 (page 5, second and third paragraphs), it appears obvious to use this promoter in an adenovirus in order to control the YB-1 replication.

V. 2. Consequently, claims 28, 29, 41 and 42 cannot be acknowledged as involving an inventive step.

V. 6. Since, as was indicated above (cf. V.), the viral oncogene in claims 30-35 is already known, it is assumed that its use according to claim 46 is obvious to a person skilled in the art. Accordingly, the subject matter of this claim does not involve an inventive step pursuant to PCT Article 33(1) and (3).

V.3.7 The subject matter of claims 56-70 differs from the use of an adenovirus proposed in D1 in that the drug also contains a combination of at least two cytostatic agents.

V. 1. The problem to be solved can be regarded as that of providing a more efficient tumor therapy agent.

V. 2. D1 also discloses the additional use of cytostatic agents ([0024, last sentence]) in the pharmaceutical compound for tumor

therapy. This statement is kept general, however, and the document does not show, for example using experimental data, that the use of this agent has a specific effect. Therefore, the prior art does not appear to contain any knowledge that would enable a person skilled in the art to reproduce the subject matter of claims 56-70, without thereby being inventive, and therefore these claims appear to meet the requirements of PCT Article 33(1) and (3).

V.4. **Remarks**

V. 1. The labels Ad24, dl922-947, E1Ad/01/07, dl1119/1131, CB016 and dl520 used in claim 27 have no generally acknowledged meaning and leave the reader uncertain as to the meaning of the technical features in question. As a result, the definition of the subject matter of this claim or these claims lacks clarity pursuant to PCT Article 6.

V. 2. Claims 60 and 61 do not meet the requirements of PCT Article 6, because the subject matter for which protection is sought is not clearly defined. The claims attempt to define the subject matter in terms of the result to be achieved: "an agent (that) influences the availability of a component of the cell..." but in so doing merely states the problem to be solved without indicating the

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

technical features necessary for achieving this result.

V. 3. The applicant should note that document WO 03099859, which was cited in the search report, will become relevant for the assessment of novelty in the regional phase.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

The sequence listing in the description, pages 1-4, received by this authority on 28.02.2005 with letter of 28.02.2005

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*